Office Action Summary	Application No.	Applicant(s)	
	09/729,478	KUSHNER ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *12,17 and 23-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-16 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group III (claims 13-16) in Paper No. 7 (16 May 2002) is acknowledged. The traversal is on the ground(s) that search of the literature for references pertinent to Group III will find references pertinent to claims of Group I and V. This argument is found to be persuasive, and Groups I, III and V (claims 1-11, 13-16, and 18-22) will be examined together.

Claims 12, 17 and 23-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made with traverse in Paper No. 7.

Claims 1-11, 13-16, and 18-22 are under examination.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). For example, see pp. 10 and 13. However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821 through 1.825 because each disclosure of a sequence embraced by the definitions set forth in the rules is not accompanied by the required reference to the relevant sequence identifier. Compliance with the sequence rules is required. Please see Notice to Comply, attached.

35 U.S.C. § 112, Second Paragraph

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/729,478	12/04/2000	Peter Kushner	407T-896330US	7340

22798 7590 06/18/2002

LAW OFFICES OF JONATHAN ALAN QUINE
P O BOX 458
ALAMEDA, CA 94501

EXAMINER
KEMMERER, ELIZABETH

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/18/2002

31

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-16, and 18-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claims are indefinite in that the recited method steps fail to achieve the desired end result stated in the preambles of the claims. The preambles of independent claims 1 and 13 recite a method for screening a test compound for the ability to activate or inhibit, respectively, transcription through an indirect estrogen response. The preamble of independent claim 18 recites a method for screening a test environmental compound for estrogenic activity. The method steps of all three claims recite providing a cell comprising a particular reporter gene construct, contacting the cell with a compound or compounds, and detecting reporter gene activity. The claims fail to recite what result is required for classifying the test compound as having the desired activity. Dependent claims 2-11, 14-16, and 19-22 are included in this rejection in that they depend from claims 1, 13, or 18 and fail to correct this deficiency.

The instant rejection can be obviated by amending the claims to recite the required result. For example, Applicant may wish to consider amending claim 1 to add a phrase to the following effect, "wherein enhanced expression of the reporter gene indicates that said test compound has agonistic estrogenic activity mediated through an indirect estrogen response." Similarly, claim 13 could be amended to recite "wherein inhibition of enhanced expression of said reporter gene produced by said compound

known to have agonistic estrogenic activity indicates that said test compound inhibits agonistic estrogenic activity mediated through an indirect estrogen response." Claim 8 also fails to recite a step wherein a particular result indicates a particular activity (i.e., there is no step wherein enhanced or inhibited expression of the second reporter gene indicates an activity). Applicant is advised that support for new claim language must clearly be identified in the specification, and the addition of new matter must be avoided.

Claims 3, 15, and 21 are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "over-expresses" is relative, and the claims fail to provide a reference or basal level of estrogen receptor expression with which the skilled artisan can compare. Thus, the claims are indefinite in that the metes and bounds of the claimed invention cannot be determined.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening a test compound for the ability to activate transcription through an indirect estrogen response, the method comprising: a) providing a cell comprising an estrogen receptor, a promoter comprising

an AP1 site which regulates expression of a reporter gene, and AP1 proteins; b) contacting the cell with the test compound; and c) detecting the expression of the reporter gene; wherein enhanced expression of the reporter gene indicates that the test compound has the ability to activate transcription through an indirect estrogen response, does not reasonably provide enablement for a method wherein the cells lack AP1 proteins. Similarly, claims 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening a test compound for the ability to inhibit transcription through an indirect estrogen response, the method comprising: a) providing a cell comprising an estrogen receptor, a promoter comprising an AP1 site which regulates expression of a reporter gene, and AP1 proteins; b) contacting the cell with the test compound and a compound known to mediate an indirect estrogen response; and c) detecting the expression of the reporter gene; wherein reduced expression of the reporter gene indicates that the test compound has the ability to inhibit transcription through an indirect estrogen response, does not reasonably provide enablement for a method wherein the cells lack AP1 proteins. Finally, claims 18-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening a test environmental compound for estrogenic activity, the method comprising: a) providing a cell comprising an estrogen receptor, a promoter comprising an AP1 site which regulates expression of a reporter gene and AP1 proteins and/or a promoter comprising an estrogen response element which regulates the expression of a reporter gene; b) contacting the cell with the test compound; and c) detecting the expression of the

reporter gene; wherein enhanced expression of the reporter gene driven by either the AP1 promoter or the estrogen response element promoter indicates that the test compound has estrogenic activity, does not reasonably provide enablement for a method wherein the cells lack AP1 proteins when the AP1 promoter is used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification clearly indicates that the cells used in the screening methods must express AP1 proteins (AP1 transcription activation factors such as Jun and Fos proteins) in order to identify even known estrogen or anti-estrogen compounds which affect transcription through an indirect estrogen response. For example, F9 cells, which do not express AP1 proteins, failed to respond to estrogen at the AP1 reporter construct (Fig. 1B). At p. 15, lines 4-5, the specification clearly states that estrogen induction at the AP1 site requires AP1 proteins. See also specification from pp. 19-20. The claimed screening methods do not recite AP1 protein expression as a requirement of the cells comprising AP1 promoters (e.g., claims 1, 13, and 19). These claims are not enabled in their full scope because it is clear that the AP1 proteins are required in order to avoid false negative results. Also, the specification is silent with regard to particular AP1 promoters which would function in the claimed assay in the absence of AP1 proteins. Due to the lack of guidance or working examples directed to the use of AP1 promoter constructs in the absence of AP1 proteins to identify compounds affecting transcription through an indirect estrogen response, the complex nature of the invention, the

unpredictability of the art, and the broad claims which fail to recite any specific AP1 promoters, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-5, 8, 9, and 13-16 are rejected under 35 U.S.C. § 102(a) as being anticipated by Philips et al (July 1993, Journal of Biological Chemistry 268:14103-8, Ref. 40 of record). Philips et al teach a method for screening a test compound for the ability to activate transcription through an indirect estrogen response (p. 14106, last sentence of column 1), the method comprising: (a) providing an MCF-7 cell which "over-expresses" the estrogen receptor and a promoter comprising a genetically engineered AP1 site which regulates the expression of a chloramphenicol acetyl transferase (CAT) reporter gene; (b) contacting the cell with a test compound; and (c) detecting the expression of the reporter gene (re: claims 1 and 3-5; p. 14105, paragraph bridging columns 1-2; Figs. 3A, 3B, and 4). Philips et al also teach this method comprising the further steps of: (a) providing a second cell (or the same cell) comprising an estrogen receptor and a promoter comprising a standard estrogen response element (ERE) from Xenopus vitellogenin A2 which regulates the expression of a second reporter gene; (b)

contacting the second cell with the test compound; and (c) detecting the expression of the second reporter gene (re: claims 8 and 9; pp. 14105-14106, "Anti-estrogens Inhibit and Estradiol Stimulates ..." and "The Anti-Growth Factor Effect ..."; Fig. 3D). Finally, Philips et al teach a method for screening a test compound for the ability to inhibit transcription through an indirect estrogen response, the method comprising: (a) providing a cell over-expressing an estrogen receptor and comprising a promoter having a genetically engineered AP1 site; (b) contacting the cell with the test compound and tamoxifen ("OHT", a compound which mediates an indirect estrogen response); and (c) detecting the expression of the reporter gene (re: claims 13-16; p. 14106, top paragraph of column 2 and p. 14107, Fig. 6). It is noted that since "over-express" is a relative term and the claims fail to recite a basal or reference level of expression, the teachings of the reference regarding MCF-7 cells meet the limitations of claims 3 and 15.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Philips et al (July 1993, Journal of Biological Chemistry 268:14103-8, Ref. 40 of record) in view of Anzai et al (1989, Cancer Research 49:2362-2365, Ref. 6 of record). As discussed above, Philips et al disclose methods for screening test compounds for the ability to activate or inhibit transcription through an indirect estrogen response.

Philips et al do not teach the use of uterine cells such as Ishikawa cells in the assay. However, it was well known in the art at the time of the invention that Ishikawa cells express estrogen receptor, and are useful in studies of anti-estrogens as taught, for example, by Anzai et al (p. 2362, last paragraph of Abstract; p. 2365, last sentence of Discussion).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the screening assay of Philips et al, and to modify that teaching by replacing the MCF-7 cells of Philips et al with the Ishikawa cells of Anzai et al with a reasonable expectation of success. The motivation to do so is provided by the teachings of the references that both MCF-7 and Ishikawa cells bear estrogen receptors, and the teaching of Anzai et al that Ishikawa cells provide a useful model to study estrogens and anti-estrogens.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Philips et al (July 1993, Journal of Biological Chemistry 268:14103-8, Ref. 40 of record) in view of Sambrook et al (1989, Molecular Cloning, pp. 16.57-16.58, Ref. 29 of record). As discussed above, Philips et al disclose methods for screening test compounds for the ability to activate or inhibit transcription through an indirect estrogen response, comprising contacting cells with test compounds wherein the cells comprise one of two estrogen responsive reporter gene constructs (i.e., the AP1 promoter driven CAT construct or the standard estrogen response element promoter driven CAT construct).

Philips et al do not teach a method wherein the two types of reporter constructs are in one cell. However, it was well known in the art at the time of the invention that co-transfection of two reporter constructs was possible, and saved steps in that a second transfection experiment was avoided. For example, Sambrook et al teach co-transfection of a CAT reporter construct and a β -galactosidase reporter construct, each driven by different promoters (p. 16.58, second full paragraph). Thus, the same group of cells could be assayed for expression driven by two different promoters.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of assaying two different reporter constructs in separate populations of cells as taught by Philips et al. and to modify that

teaching by co-transfecting two reporter constructs into one population of cells as taught by Sambrook et al, with a reasonable expectation of success. The motivation to do so is provided by the teaching of Sambrook et al regarding the benefits of assaying one population of cells for expression from two different promoters, and the recognition by the routineer that the co-transfection approach would avoid transfecting a second population of cells.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claims 18, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Philips et al (July 1993, Journal of Biological Chemistry 268:14103-8, Ref. 40 of record) in view of Wolff et al (April 1993, Journal of the National Cancer Institute 85:648-652, Ref. 39 of record). As discussed above, Philips et al disclose methods for screening test compounds for the ability to activate or inhibit transcription through an indirect estrogen response comprising testing whether the compound can drive expression of a CAT reporter gene under the control of a promoter comprising an AP1 site. Philips et al also discuss the link between compounds which activate transcription from genes driven by estrogen responsive promoters and breast cancer (p. 14102, paragraph bridging columns 1-2 to 14107, last paragraph of Discussion section).

Philips et al do not disclose screening test environmental compounds for direct or indirect estrogenic activity using their screening assay. However, it was well known in

the art at the time of the invention that determination of the estrogenic properties of environmental factors is critical since many environmental compounds having estrogenic activity are linked to disease. For example, Wolff et al disclose that serum levels of DDE, a major metabolite of the environmental compound DDT, is strongly linked to the incidence of breast cancer in women, thus strongly suggesting that this compound be avoided as a routinely used insecticide (p. P. 648, Abstract and column 3 first full paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the assay for screening compounds for estrogenic activity disclosed by Philips et al, and to modify that teaching by screening environmental compounds for such activity, with a reasonable expectation of success. The motivation to do so is provided by Wolff et al, who identify an environmental estrogenic compound DDE which is strongly linked to breast cancer. The skilled artisan would have appreciated that the screening assay of Philips et al would have been a convenient way of identifying environmental compounds having estrogenic activity which could then be screened in a long-term disease etiology study for effects on estrogen-linked diseases such as breast cancer.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Philips et al (July 1993. Journal of Biological Chemistry 268:14103-8. Ref. 40 of record) in view

of Wolff et al (April 1993, Journal of the National Cancer Institute 85:648-652, Ref. 39 of record) as applied to claims 18, 20, and 21 above, and further in view of Sambrook et al (1989, Molecular Cloning, pp. 16.57-16.58, Ref. 29 of record). As discussed above, Philips et al in view of Wolff et al teach a method for screening a test environmental compound for estrogenic activity by testing its ability to activate transcription from a reporter construct driven by a promoter comprising an estrogen response element (AP1 or a standard estrogen response element, each construct being present in a separate population of cells).

Neither Philips et al nor Wolff et al teach a method wherein two different estrogen response promoters drive the expression of two different reporter genes in the same cell. However, it was well known in the art at the time of the invention that co-transfection of two reporter constructs was possible, and saved steps in that a second transfection experiment was avoided. For example, Sambrook et al teach co-transfection of a CAT reporter construct and a -galactosidase reporter construct, each driven by different promoters (p. 16.58, second full paragraph). Thus, the same group of cells can be assayed for expression driven by two different promoters.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of assaying environmental compounds for the ability to activate transcription from two different reporter constructs in separate populations of cells as taught by Philips et al in view of Wolff et al, and to modify that teaching by co-transfecting two reporter constructs into one population of cells as taught by Sambrook et al, with a reasonable expectation of success. The

motivation to do so is provided by the teaching of Sambrook et al regarding the benefits of assaying one population of cells for expression from two different promoters, and the recognition by the routineer that the co-transfection approach would avoid the necessity of transfecting a second population of cells.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Philips et al (July 1993, Journal of Biological Chemistry 268:14103-8, Ref. 40 of record) in view of Wolff et al (April 1993, Journal of the National Cancer Institute 85:648-652, Ref. 39 of record) as applied to claims 18, 20, and 21 above, and further in view of Kushner et al (1990, Molecular Endocrinology 4:1465-1473, Ref. 18 of record). As discussed above, Philips et al in view of Wolff et al teach a method for screening a test environmental compound for estrogenic activity by testing its ability to activate transcription from a reporter construct driven by a promoter comprising an estrogen response element (AP1 or a standard estrogen response element, each construct being present in a separate population of cells). The cells used by Philips et al are MCF-7 cells, which bear estrogen receptors.

Neither reference suggests using ERC1 cells. However, these cells were known in the art to bear large numbers of estrogen receptors (for example, as disclosed by Kushner et al, p. 1469, paragraph bridging columns 1-2 and Table 3), and thus would have been useful in the assay taught by Philips et al in view of Wolff et al.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of assaying environmental compounds for the ability to activate transcription from two different reporter constructs in separate populations of cells as taught by Philips et al in view of Wolff et al, and to modify that teaching by substituting ERC1 cells as taught by Kushner for the MCF-7 cells taught by Philips et al, with a reasonable expectation of success. The motivation to do so is provided by the teaching of Philips et al and Kushner et al that both MCF-7 cells and ERC1 cells bear estrogen receptors and are useful in assays for estrogen or anti-estrogen compounds, and the teaching of Kushner et al that the ERC1 cells express estrogen receptor at high levels.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claims 1, 3-5, 8, 9, and 13-16 are rejected under 35 U.S.C. § 103 as being unpatentable over Pons et al (1990, BioTechniques 9:450-459, Ref. 28 of record) in view of Gaub et al. (1990, Cell 63:1267-1276, Ref. 14 of record). Pons et al teach a screening method wherein compounds which activate or inhibit transcription, via a direct estrogen response, from a reporter gene genetically engineered to comprise a promoter having an ERE (estrogen responsive element) from the Xenopus vitellogenin A2 gene (p. 450, paragraph bridging columns 2-3). The cells expressing the reporter construct were MCF-7 cells, which "over-express" estrogen receptor (it is noted that since "over-express" is a relative term and the claims fail to recite a basal or reference level of

expression, the teachings of the reference meet the limitations of the claims). Tamoxifen is one of the known anti-estrogen compounds assayed ("OH-Tam"; p. 454, "Response of Stable Transfectants...").

Pons et al do not teach a screening method wherein an indirect estrogen response is measured by a compound's ability to activate or inhibit transcription of a reporter construct comprising an AP1 site. However, Gaub et al teach that there is an indirect estrogen response (p. 1268, middle of column 1), and that it is attributable to activation at AP1 sites (p. 1271, middle paragraph of column 2; p. 1272, first full paragraph of second column).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the direct (classical) estrogen response screening method of Pons et al., and to modify that teaching by screening for compounds acting through the AP1-mediated indirect estrogen response taught by Gaub et al. with a reasonable expectation of success. The routineer would have been motivated to do so given the knowledge that many "anti-estrogens" are of limited therapeutic value because they have both estrogen antagonist and estrogen agonist activities, that a therapeutically valuable "pure" anti-estrogen would have been expected to inhibit transcription by both the direct and indirect estrogen response pathways, and that screening compounds for the ability to inhibit transcription through both a direct and indirect estrogen response pathway would have identified such pure anti-estrogen compounds.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claims 2, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pons et al (1990, BioTechniques 9:450-459, Ref. 28 of record) in view of Gaub et al. (1990, Cell 63:1267-1276, Ref. 14 of record) as applied to claims 1, 3-5, 8, 9, and 13-16 above, and further in view of Anzai et al (1989, Cancer Research 49:2362-2365, Ref. 6 of record). As discussed above, Pons et al. taken with Gaub et al. teach a screening method to identify compounds activating or inhibiting transcription of a reporter construct driven by a promoter comprising either a standard estrogen response element or an AP1 site, indicative of the compounds' roles in the direct and indirect estrogen response. Pons et al teach the use of MCF-7 cells in the assay, which bear estrogen receptors.

Neither Pons et al nor Gaub et al teach the method wherein the cells are of uterine origin, such as Ishikawa cells. However, it was well known in the art that Ishikawa cells express estrogen receptor, and are useful in studies of anti-estrogens (p. 2362, last paragraph of Abstract; p. 2365, last sentence of Discussion).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the screening assay of Pons et al in view of Gaub et al, and to modify that teaching by replacing the MCF-7 cells of Pons et al with the Ishikawa cells of Anzai et al with a reasonable expectation of success. The motivation to do so is provided by the teachings of the references that both MCF-7 and Ishikawa

cells bear estrogen receptors, and the teaching of Anzai et al that Ishikawa cells provide a useful model to study estrogens and anti-estrogens.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pons et al (1990, BioTechniques 9:450-459, Ref. 28 of record) in view of Gaub et al. (1990, Cell 63:1267-1276, Ref. 14 of record) as applied to claims 1, 3-5, 8, 9, and 13-16 above, and further in view of Sambrook et al (1989, Molecular Cloning, pp. 16.57-16.58, Ref. 29 of record). As discussed above, Pons et al. taken with Gaub et al. teach a screening method to identify compounds activating or inhibiting transcription of a reporter construct driven by a promoter comprising either a standard estrogen response element or an AP1 site, indicative of the compounds' roles in the direct and/or indirect estrogen response.

Neither reference teaches a method wherein the two reporter constructs are present in the same cell. However, it was well known in the art at the time of the invention that co-transfection of two reporter constructs was possible, and saved steps in that a second transfection experiment was avoided. For example, Sambrook et al teach co-transfection of a CAT reporter construct and a -galactosidase reporter construct, each driven by different promoters (p. 16.58, second full paragraph). Thus, the same group of cells can be assayed for expression driven by two different promoters.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of assaying compounds for the ability to activate transcription from two different estrogen responsive reporter constructs in separate populations of cells as taught by Pons et al in view of Gaub et al, and to modify that teaching by co-transfecting two reporter constructs into one population of cells as taught by Sambrook et al, with a reasonable expectation of success. The motivation to do so is provided by the teaching of Sambrook et al regarding the benefits of assaying one population of cells for expression from two different promoters, and the recognition by the routineer that the co-transfection approach would avoid transfecting a second population of cells.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claims 18, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pons et al (1990, BioTechniques 9:450-459, Ref. 28 of record) in view of Gaub et al. (1990, Cell 63:1267-1276, Ref. 14 of record) as applied to claims 1, 3-5, 8, 9, and 13-16 above, and further in view of Wolff et al (April 1993, Journal of the National Cancer Institute 85:648-652, Ref. 39 of record). As discussed above, Pons et al taken with Gaub et al teach a screening method to identify compounds activating or inhibiting transcription of a reporter construct driven by a promoter comprising either a standard estrogen response element or an AP1 site, indicative of the compounds' roles in the direct and/or indirect estrogen response. Pons et al also discuss the link between

estrogenic compounds and hormone responsive tumors (p. 450, first sentence of Introduction). Gaub et al use CAT as a convenient reporter gene (p. 1274, middle paragraph of column 1).

Neither Pons et al nor Gaub et al disclose screening test environmental compounds for direct or indirect estrogenic activity using their screening assay. However, it was well known in the art at the time of the invention that determination of the estrogenic properties of environmental factors is critical since many environmental compounds having estrogenic activity are linked to disease. For example, Wolff et al disclose that levels of DDE, a major metabolite of the environmental compound DDT, is strongly linked to the incidence of breast cancer in women, thus strongly suggesting that this compound be avoided as a routinely used insecticide (p. P. 648, Abstract and column 3 first full paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the assay for screening compounds for estrogenic activity disclosed by Pons et al in view of Gaub et al, and to modify that teaching by screening environmental compounds for such activity, with a reasonable expectation of success. The motivation to do so is provided by Wolff et al, who identify an environmental estrogenic compound DDE which is strongly linked to breast cancer. The skilled artisan would have appreciated that the screening assay of Pons et al and Gaub et al would have been a convenient way of identifying environmental compounds having estrogenic activity which could then be screened for effects on estrogen-linked diseases such as breast cancer.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art..

Claim 19 is rejected under 35 U.S.C. § 103 as being unpatentable over Pons et al (1990, BioTechniques 9:450-459, Ref. 28 of record) in view of Gaub et al. (1990, Cell 63:1267-1276, Ref. 14 of record) and further in view of Wolff et al (April 1993, Journal of the National Cancer Institute 85:648-652, Ref. 39 of record) as applied to claims 18, 20, and 21 above, and further in view of Sambrook et al (1989, Molecular Cloning, pp. 16.57-16.58, Ref. 29 o record). As discussed above, Pons et al in view of Gaub et al and further in view of Wolff et al teach a method for screening a test environmental compound for estrogenic activity by testing its ability to activate transcription from a reporter construct driven by a promoter comprising an estrogen response element (AP1 or a standard estrogen response element, each construct being present in a separate population of cells).

None of Pons et al, Gaub et al, nor Wolff et al teach a method wherein two different estrogen response promoters drive the expression of two different reporter genes in the same cell. However, it was well known in the art at the time of the invention that co-transfection of two reporter constructs was possible, and saved steps in that a second transfection experiment was avoided. For example, Sambrook et al teach co-transfection of a CAT reporter construct and a -galactosidase reporter construct, each driven by different promoters (p. 16.58, second full paragraph). Thus,

the same group of cells can be assayed for expression driven by two different promoters.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of assaying environmental compounds for the ability to activate transcription from two different reporter constructs in separate populations of cells as taught by Pons et al in view of Gaub et al and further in view of Wolff et al, and to modify that teaching by co-transfecting two reporter constructs into one population of cells as taught by Sambrook et al, with a reasonable expectation of success. The motivation to do so is provided by the teaching of Sambrook et al regarding the benefits of assaying one population of cells for expression from two different promoters, and the recognition by the routineer that the co-transfection approach would avoid transfecting a second population of cells.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pons et al (1990, BioTechniques 9:450-459, Ref. 28 of record) in view of Gaub et al. (1990, Cell 63:1267-1276, Ref. 14 of record) and further in view of Wolff et al (April 1993, Journal of the National Cancer Institute 85:648-652, Ref. 39 of record) as applied to claims 18, 20, and 21 above, and further in view of Kushner et al (1990, Molecular Endocrinology 4:1465-1473, Ref. 18 of record). As discussed above, Pons et al in view of Gaub et al and further in view of Wolff et al teach a method for screening a test environmental

compound for estrogenic activity by testing its ability to activate transcription from a reporter construct driven by a promoter comprising an estrogen response element (AP1 or a standard estrogen response element, each construct being present in a separate population of cells). The cells used by Pons et al are MCF-7 cells, which bear estrogen receptors.

Neither Pons et al nor Gaub et al nor Wolff et al suggest using ERC1 cells. However, these cells were known in the art to bear estrogen receptors (for example, as disclosed by Kushner et al, p. 1469, paragraph bridging columns 1-2 and Table 3), and thus would have been useful in the assay taught by Pons et al in view of Gaub et al and further in view of Wolff et al.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of assaying environmental compounds for the ability to activate transcription from two different reporter constructs in separate populations of cells as taught by Pons et al in view of Gaub et al and further in view of Wolff et al, and to modify that teaching by substituting ERC1 cells as taught by Kushner for the MCF-7 cells taught by Pons et al, with a reasonable expectation of success. The motivation to do so is provided by the teaching of Pons et al and Kushner et al that both MCF-7 cells and ERC1 cells bear estrogen receptors and are useful in assays for estrogen or anti estrogen compounds, and the teaching of Kushner et al that the ERC1 cells express estrogen receptor at high levels.

Thus, the claimed invention as a whole was very clearly prima facie obvious over the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-11, 13-16 and 18-22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 5,723,291. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented methods are slightly narrower in scope than the pending method claims. A species renders obvious its genus. Furthermore, the dependent claims in the instant application point to the preferred embodiment in the patented claims

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number

is (703) 308-2673. The examiner can normally be reached on Mon.-Thurs. and alternate Fri., 6:30-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D. can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C Kemmerer

ECK
June 17, 2002

ELIZABETH KEMMERER
PRIMARY EXAMINER